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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 December 1998 (14.12.98)	
International application No. PCT/EP98/02998	**Applicant's or agent's file reference** P70922WO
International filing date (day/month/year) 13 May 1998 (13.05.98)	**Priority date** (day/month/year) 13 May 1997 (13.05.97)
Applicant CAWTHORNE, Michael, Anthony et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 November 1998 (23.11.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Eugénia Santos

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LUNT, Mark G.F.
Dibb Lupton Alsop
Fountain Precinct
Balm Green
Sheffield S1 1RZ
GRANDE BRETAGNE

MGL

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	11.08.99

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
P70922WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/02998	13/05/1998	13/05/1997

Applicant
SOCIETE DE CONSEILS DE RECHERCHES ET...et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office	THORNTON, J

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P70922WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/02998	13/05/1998	13/05/1997
International Patent Classification (IPC) or national classification and IPC A61K38/31		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET...et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/11/1998	11.08.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich	Authorized officer Laffargue-Haak, T

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/02998

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-17,19	as originally filed			
18	as received on	26/06/1999	with letter of	22/06/1999

Claims, No.:

1-31	as received on	26/06/1999	with letter of	22/06/1999

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 31.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does

not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 31 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5, 10-26
	No:	Claims	1, 2, 6-9
Inventive step (IS)	Yes:	Claims	----
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	27-30
	No:	Claims	1-26

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description. are made:

see separate sheet

Section I

Amended claim 1 goes beyond the disclosure of the international application as filed. The basis for new claim 1, cited by the applicant (p. 2 and 3 of the specification), refers to prior art and not to the invention. Substantive examination has therefore been carried out on claim 1 as originally filed. Amended claims 2-31 are allowable under Art. 19(2) PCT and are the basis of the present IPER.

Reference to Fig. 1 and 2 (which are not part of the application as originally filed) has been deleted on amended page 18.

Section III

Claim 31 has no own technical features but refers only to the description.

Section V

New documents cited (Ref 17 and 34 of article of Møller et al. 1988)

POINTER J, HENGL G, BAYER PJM, FLEGEL U.: "Somatostatin inhibits the increase of serum triglyceride concentration following a test meal.", SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY 1976, vol. 2, page 51.

NAKABAYSHI H, SAGARA H, USUKURA N, YOSHIMITSU K, IMAMURA T, SETA T, YANASE E, KAWATO M, HIRAIWA Y, SAKATO S, TAKEDA R.: "Effect of somatostatin on the flow rate and triglyceride levels of thoracic duct lymph in normal and vagotomized dogs", DIABETES, 1981, vol. 30, pages 440 to 445.

GINSBERG HN, JACOBS A, LE N-A, SANDLER J. "Effect of somatostatin-induced suppression of postprandial insulin response upon the hypertriglyceridemia associated with a high carbohydrate diet." JOURNAL OF CLINICAL INVESTIGATION 1982, vol. 70, pages 1225 to 1233.

Novelty

Møller et al. (Clin Science, 1988, 345-350 discloses the use of a somatostatin analogue SMS 201-995 for lowering triglyceride levels (p. 348, Fig. 5) and blood glycerol levels (Fig. 4). According to Table II (p. 17) of WO 96/35950, this compound has a K_i of 7.0 nM for SSTR-5 receptor (ratio SSTR-2/SSTR-5=0.07) and can therefore be considered as a non-selective somatostatin type 5 receptor agonist. The above cited document therefore seems to anticipate the subject-matter of claims 1, 6 and 8.

Pointer et al. disclose that somatostatin-14 suppresses the rise in serum triglyceride after ingestion of fat (abstract). Similar observation have been made by Nakabayashi et al. (see abstract). According to WO 96/35950 (K_i for SSTR-5 = 0.88 nM ; ratio SSTR-2/SSTR-5=0.20, see Table II) and the description of the present application (p. 9, l. 19-24), somatostatin-14 can be considered as a selective somatostatin type-5 receptor agonist. Pointer et al. and Nakabayashi et al. therefore seem to anticipate the subject-matter of claims

1, 2, 6-9 and 27-30. 27-28

WO 96/35950 (p. 7, l. 26-p. 9. l.10) and WO 97/11962 (see Table 1. p. 14) disclose several selective somatostatin type-5 receptor agonists and appear to anticipate the amended claims 27 and 28.

Ginsberg et al. disclose that somatostatin (= selective somatostatin type 5 receptor agonist) does not suppress the rise in plasma triglycerides associated with a high carbohydrate meal in non-diabetic subjects. This document seems to anticipated the subject of amended claims 27 and 28.

Amended claims 27 and 28 ("A pharmaceutical composition *for the treatment of hyperlipidemia* ...") refer to a first medical use of somatostatin type-5 receptor selective agonists and no longer to a pharmaceutical composition (= subject of old claims 27 and 28). This implies that *any medical use* of these agonists (e.g. Pointer et al., Nakabayshi et al., Ginsberg et al.) or *any pharmaceutical composition* comprising these agents (e.g. WO 96/35950 or WO 97/11962) is novelty destroying for these claims.

Inventive step

The publication of Møller et al., disclosing the use of mixed SSTR-2/SSTR-5 agonists (e.g. SMS 201-995 or somatostatin-14) for the treatment of hyperlipidaemia, can be considered as the closest prior art. The difference with the present application is the use of *highly* selective SSTR-5 agonists (e.g. ratio SSTR-2/SSTR-5 > 2). The technical problem to be solved seems to be "to provide alternative (highly selective) SSTR-5 agonists useful for the treatment of hyperlipidaemia". As the prior art already discloses several somatostatin analogues with these ratios (Table II of WO 96/35950 and Table 1 of WO 97/11962), it appears to be obvious for the skilled man to test whether these or related compounds have any pharmacological effect on blood lipid levels.

Industrial applicability

For the assessment of the present claims 1-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment (i.e. amended claims 27, 28) and the use of such a compound for the manufacture of a medicament for a new medical treatment (i.e. amended claims 29, 30).

Section VI

WO 98 10786, filed 4 September 1996 and published on 3 April 1997 claims a priority dates of 26 and 29 September 1995.

Section VIII

The expression "Tyr(I)" used in claims 23-26, appears not to be defined in the description.

Hayward's Heath, W. Sussex, U.K.) and heparin (Sigma Chemical Co., Poole, Dorset, U.K.) were added to the blood samples to a final concentration of 400 KIU/ml and 100 units/ml, respectively. Plasma fractions were prepared from these samples by centrifugation at 400 x G in a microfuge, for the estimation of triglycerides and glycerol. Samples were then stored at -80°C until assayed.

Plasma glycerol and triglycerides were determined using the Sigma Enzymatic (Tinder) calorimetric assay kit (Cat #337-B, Sigma Chemical Co., Poole, Dorset, U.K.) and measuring absorbance at 540 nm in a spectrophotometer.

After 6 days of treatment with BIM-23268C at 3 mg/kg, twice a day by subcutaneous injection, both plasma glycerol and triglycerides were significantly lowered, as exemplified by the samples taken at time 30 and 60 min. before the oral glucose challenge. The administration of an oral glucose challenge had no significant effect on plasma lipids. The BIM-23268C treated group showed significantly lower plasma glycerol and triglycerides through the 2-hour test period. The results suggested that BIM-23268C, following a 6-day treatment period at the prescribed dose was effective in reducing hypertriglyceridemia.

Measure of Efficacy in Patient

The effect of the somatostatin agonist will be assessed for a reduction in total cholesterol, total triglycerides, and total LDL cholesterol (e.g., as described in Dubrey, S.W., et al., Diabetes 43:831-835

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426 Rec'd PCT/PTO 10 NOV 1999

CLAIMS

1. A method of treating hyperlipidemia in a patient due diabetes mellitus, hypothyroidism, uremia, nephrotic syndrome, acromegaly, obstructive liver disease, dysproteinemia, drugs or genetic disorders said method comprising administering a therapeutically effective amount of a somatostatin type-5 receptor agonist to said patient.

2. A method of treating hyperlipidemia in a patient, said method comprising administering a therapeutically effective amount of a somatostatin type-5 receptor agonist to said patient, wherein said somatostatin type-5 receptor agonist has a Ki of less than 2 nM for the somatostatin type-5 receptor.

3. A method of treating hyperlipidemia in a patient, said method comprising administering a therapeutically effective amount of a somatostatin type-5 receptor selective agonist to said patient.

4. A method of claim 2, wherein said somatostatin type-5 receptor selective agonist has a Ki for the type-5 somatostatin receptor that is at least 10 times less than its Ki for the somatostatin type-2 receptor.

5. A method of treating hyperlipidemia in a patient, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, where a disulfide bond exists between the free thiols of the two Cys residues, or H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2.

6. A method according to claim 1, of lowering the amount of triacylglycerols, glycerol, or cholesterol in the blood of a patient.

7. A method of lowering the amount of triacylglycerols, glycerol, or cholesterol in the blood of a patient, said method comprising administering a therapeutically effective amount of a somatostatin type-5 receptor selective agonist to said patient.

8. A method of claim 6, wherein said method comprises lowering the amount of triacylglycerols in said patient.

9. A method of claim 8, wherein said somatostatin type-5 receptor agonist has a Ki of less than 2 nM for the somatostatin type-5 receptor.

10. A method of claim 7, wherein said method comprises lowering the amount of triacylglycerols in said patient.

11. A method of claim 10, wherein said somatostatin type-5 receptor selective agonist has a Ki for the type-5 somatostatin receptor that is at least 10 times less than its Ki for the somatostatin type-2 receptor.

12. A method of claim 8, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, where a disulfide bond exists between the free thiols of the two Cys residues, or H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2.

13. A method of claim 6, wherein said method comprises lowering the amount of glycerol in said patient.

14. A method of claim 13, wherein said somatostatin type-5 receptor agonist has a Ki of less than 2 nM for the somatostatin type-5 receptor.

15. A method of claim 7, wherein said method comprises lowering the amount of glycerol in said patient.

16. A method of claim 15, wherein said somatostatin type-5 receptor selective agonist has a Ki for the type-5 somatostatin receptor that is at least 10 times less than its Ki for the somatostatin type-2 receptor.

17. A method of claim 13, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, where a disulfide bond exists between the free thiols of the two Cys residues, or H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2.

18. A method of claim 6, wherein said method comprises lowering the amount of cholesterol in said patient.

19. A method of claim 18, wherein said somatostatin type-5 receptor agonist has a Ki of less than 2 nM for the somatostatin type-5 receptor.

20. A method of claim 7, wherein said method comprises lowering the amount of total cholesterol or LDL cholesterol in said patient.

21. A method of claim 20, wherein said somatostatin type-5 receptor selective agonist has a Ki for the type-5 somatostatin receptor that is at least 10 times less than its Ki for the somatostatin type-2 receptor.

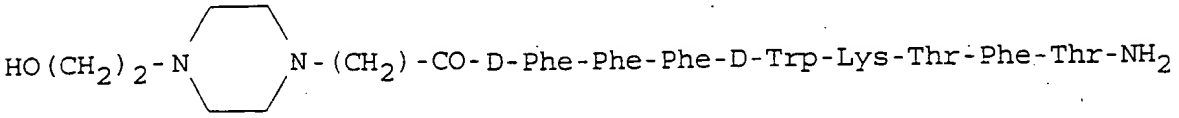
22. A method of claim 18, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, where a disulfide bond exists between the free thiols of the two Cys residues, or H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2.

23. A method according to claim 1 wherein the somatostatin type-5 receptor agonist is

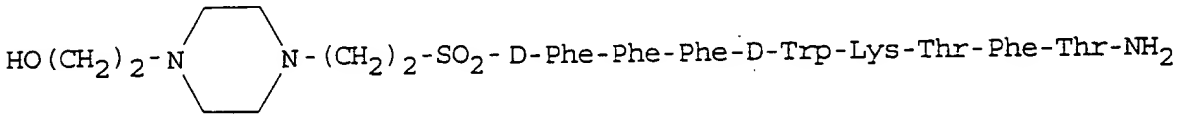
H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,



or

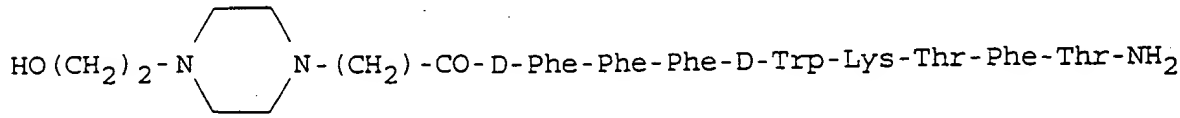


24. A method according to claim 7 wherein the somatostatin type-5 receptor agonist is

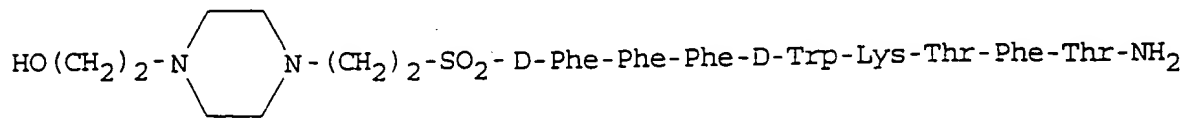
H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,



or

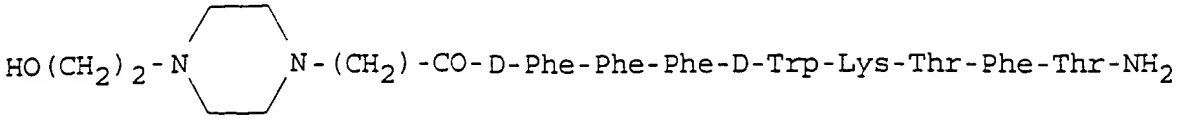


25. A method according to claim 13 wherein the somatostatin type-5 receptor agonist is

H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,

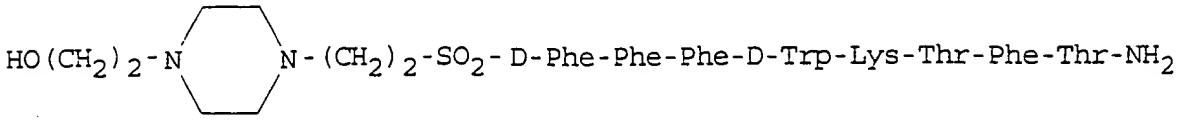
H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,



$HO(CH_2)_2$-N N-(CH_2)-CO-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

or



$HO(CH_2)_2$-N N-$(CH_2)_2$-SO_2-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

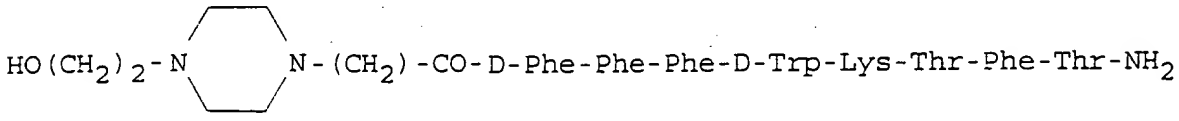
.

26. A method according to claim 18 wherein the somatostatin type-5 receptor agonist is

H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,

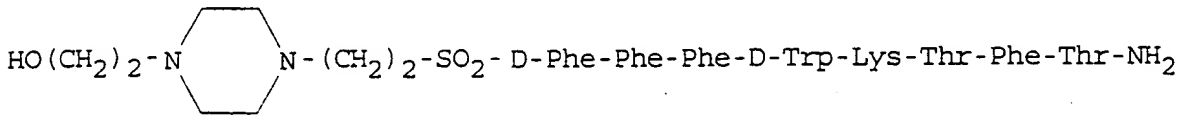
H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,



$HO(CH_2)_2$-N N-(CH_2)-CO-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

or



$HO(CH_2)_2$-N N-$(CH_2)_2$-SO_2-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

.

27. A pharmaceutical composition for the treatment of hyperlipidemia comprising a therapeutically effective amount of a somatostatin type-5 receptor, selective agonist.

28. A pharmaceutical composition as claimed in claim 27, said agonist having the features identified in any one of claims 2, 4, 5 and 23 to 26.

29. Use of a somatostatin type-5 receptor selective agonist in the formulation of a pharmaceutical composition for use in treating hyperlipidemia, in a human or mammalian animal.

30. Use of a somatostatin agonist according to claim 29, wherein said somatostatin agonist has the relevant features identified in any one of claims 2, 4, 5 and 23 to 26.

31. A pharmaceutical composition substantially as hereinbefore described with reference to the Examples.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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08/855,311 13 May 1997 (13.05.97) US

(71) Applicant *(for all designated States except US)*: SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES S.A. (S.C.R.A.S.) [FR/FR]; 51–53, rue du Docteur Blanche, F–Paris (FR).

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(74) Agent: LUNT, Mark, George, Francis; Dibb Lupton Alsop, Fountain Precinct, Balm Green, Sheffield S1 1RZ (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD AND COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND OTHER CONDITIONS

(57) Abstract

The present invention relates to a method of treating hyperlipidemia and to reducing triacylglycerols, glycerol and cholesterol in a patient. The method includes the step of administering a therapeutically effective amount of a type–5 selective somatostatin agonist to said patient. A pharmaceutical composition comprises said agonist and such product is used in the preparation of the composition for use in treating hyperlipidemia or reducing triacylglycerols, glycerol and cholesterol in a patient's body.

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METHOD AND COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND OTHER CONDITIONS

This invention relates to a method and to compositions useful in the treatment of hyperlipidemia and other conditions, for example high levels of triacylglycerols, glycerol or cholesterol in a patient.

BACKGROUND OF THE INVENTION

There are substantial epidemiologic, clinical, genetic and experimental evidence that suggested a primary role of plasma lipids and lipoproteins in atherogenesis (Adult Treatment Panel II, Circulation 89:1333-1445 (1994); Havel, R.J., Clin. Exp. Hypertens. 11:887-900 (1989)). Atherogenesis is the process by which lipids accumulate in the intimal lining of arteries leading to the formation of plaques and hardening of the vessel wall or atherosclerosis. Although the exact mechanism leading to atherogenesis is still not well understood, abnormalities of lipid and lipoprotein metabolism, coagulation, hyperinsulinism and glycation all seem to contribute significantly to the process (Bierman, E.L., Arterio. Throm. 12:647-656 (1992)). Hyperlipidemia's characteristics of raised plasma concentrations of triglyceride, raised low density lipoprotein (LDL) cholesterol concentrations, and low concentrations of high density lipoprotein (HDL) cholesterol are known independent risk factors for atherosclerosis and its clinical sequelae, ischemic heart disease or coronary heart disease (Harrison's Principles

of Internal Medicine, Eds. Braunwald, E., et al., 11th Edition, McGraw-Hill, 1016-1024 (1988); Reaven, GM, et al., N. Engl. J. Med. 334:374-381 (1996); and Hamsten, A., et al., N. Engl. J. Med. 313:1557-1563 (1985)). Hyperlipidemia in clinical practice, defined by the upper 10 percent of the distribution of plasma lipid levels in a population, i.e., serum cholesterol of 205 mg/dl or higher, serum triglycerides of 200 mg/dl, is usually recommended for treatment (Havel, R.J., et al., N. Engl. J. Med. 332:1491-1498 (1995)). Routine measurements of concentrations of cholesterol and triacylglycerides in the plasma have become widespread in clinical practice which permits the identification of patients with asymptomatic hyperlipidemia. Guidelines are available for diagnosis and monitoring responses to therapy. See Workshop Treatment of Hyperlipidemia, 1996-2 (Lakesmedelsverket, Uppsala, Sweden 1996). Lowering plasma lipid concentrations reduces the amount of atherogenic plaques on the intima of blood vessels (Pathologic Basis of Disease, Eds. S.L. Robbins, et al., 3rd Edition, W.B. Saunders 506-518 (1984); Levine, G.N., et al., N. Engl. J. Med. 332:512-521 (1995)).

A number of disorders are associated with hyperlipidemia, such as uncontrolled diabetes mellitus (insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus) (Bianchi, R., et al., Diab. Nutr. Metabl. 7:43-51 (1994); Welborn, T.A., Aust. NZ J. Med. 24:61-64 (1994)), hypothyroidism, uremia, nephrotic syndrome, acromegaly, obstructive liver disease, dysproteinemia (multiple myeloma, lupus erythematosus)

(Harrison's Principles of Internal Medicine, Ed. Braunwald, E., et al., 11th Edition, McGraw-Hill 1016-1024 (1988)). A number of drugs also produce hyperlipidemia, such as oral contraceptives, estrogens, glucocorticoids and antihypertensives. Dietary factors such as increased caloric intake (recent weight gain), consumption of foods high in saturated fats and cholesterol and alcohol intake contribute to the development of hyperlipidemia. Aside from these, primary hyperlipidemia include a family of genetic disorders associated with family histories of hyperlipidemia or xanthomas and pancreatitis.

The administration of somatostatin has been shown to reduce plasma triglyceride concentrations in alloxan diabetic dogs (Martin, C., et al., Life Sci. 35:2627-2633 (1984)), normal humans (Moller, N., et al., Clin. Sci., 75:345-350 (1988); Fukushima, H., et al., Endocrinol. Japan., 32:241-248 (1985)) and acromegalics (Cohen, R., et al., Horm. Metab. Res., 24:397-400 (1992); James, R.A., et al., Diabet. Med. 8:517 (1991). Five distinct somatostatin receptor subtypes have been isolated. While the somatostatin type-5 receptor has been found in various areas of the brain, it has not been found in the major tissues associated with lipid metabolism, such as the liver, pancreas, and muscle. See, Bruno, et al., Endocrinology 133:2561 (1993). The present invention relates to the discovery that the somatostatin type-5 receptor is responsible for this reduction of plasma lipids.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating hyperlipidemia in a patient (e.g., a mammal such as a human). The method includes the step of administering a therapeutically effective amount of a somatostatin type-5 receptor (SSTR-5) agonist (e.g., a somatostatin type-5 selective agonist) to said patient. The present invention also relates to a method of lowering the amount of cholesterol (e.g., total cholesterol or LDL cholesterol), triacylglycerols (e.g, triglycerides), or glycerol in a patient. The method includes the step of administering a therapeutically effective amount of a somatostatin type-5 receptor (SSTR-5) agonist to said patient (e.g., a somatostatin type-5 receptor selective agonist). The somatostatin agonist may be administered parenterally, e.g., administered intravenously, subcutaneously, or by implantation of a sustained release formulation. In one embodiment, the patient is suffering from hyperlipidemia (e.g., abnormally high levels of cholesterol, triacylglycerols, or glycerol) and/or is a diabetic (i.e., type-I or type-II diabetic).

The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a somatostatin type-5 receptor, optionally selective, agonist. The invention also provides the use of such agonist in the preparation of such composition for the treatment of hyperlipidemia and/or reduction in levels of triacylglycerols, glycerol or cholesterol in a human or mammalian animal.

Definitions of "somatostatin type-5 receptor agonist" and "somatostatin type-5 receptor selective agonist" will be given below. A therapeutically effective amount depends upon the condition being treated, the route of administration chosen, and the specific activity of the compound used and ultimately will be decided by the attending physician or veterinarian (e.g., between 5 :g/day and 5 mg/day). In one embodiment, the somatostatin agonist is administered to the patient until the patient's lipid levels (e.g., glycerol, triacylglycerols, or cholesterol) decrease. In another embodiment, the somatostatin agonist is administered for the lifetime of the patient.

The somatostatin agonist may be injected parenterally, e.g., intravenously, into the bloodstream of the subject being treated. However, it will be readily appreciated by those skilled in the art that the route, such as intravenous, subcutaneous, intramuscular, intraperitoneal, enterally, transdermally, transmucously, sustained released polymer compositions (e.g., a lactic acid polymer or lactic acid and glycolic acid copolymer microparticle or implant), profusion, nasal, oral, etc., will vary with the condition being treated and the activity and bioavailability of the somatostatin agonist being used.

While it is possible for the somatostatin agonist to be administered as the pure or substantially pure compound, it may also be presented as a pharmaceutical formulation or preparation. The formulations to be used

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in the present invention, for both humans and animals, comprise any of the somatostatin agonists to be described below, together with one or more pharmaceutically acceptable carriers thereof, and optionally other therapeutic ingredients.

The carrier must be "acceptable" in the sense of being compatible with the active ingredient(s) of the formulation (e.g., capable of stabilizing peptides) and not deleterious to the subject to be treated. Desirably, the formulation should not include oxidizing agents or other substances with which peptides are known to be incompatible. For example, somatostatin agonists in the cyclized form (e.g., internal cysteine disulfide bond) can be oxidized; thus, the presence of reducing agents as excipients could lead to an opening of the cysteine disulfide bridge. On the other hand, highly oxidative conditions can lead to the formation of cysteine sulfoxide and to the oxidation of tryptophane. Consequently, it is important to carefully select the excipient. pH is another key factor, and it may be necessary to buffer the product under slightly acidic conditions (pH 5 to 6).

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient(s) into association with the carrier which constitutes one or more accessory ingredients.

In general, the formulations for tablets or powders are prepared by uniformly and intimately blending

the active ingredient with finely divided solid carriers, and then, if necessary, as in the case of tablets, forming the product into the desired shape and size.

Formulations suitable for parenteral (e.g., intravenous) administration, on the other hand, conveniently comprise sterile aqueous solutions of the active ingredient(s). Preferably, the solutions are isotonic with the blood of the subject to be treated. Such formulations may be conveniently prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering said solution sterile. The formulation may be presented in unit or multi-dose containers, for example, sealed ampoules or vials.

Formulations suitable for sustained release parenteral administrations (e.g., biodegradable polymer formulations such as polyesters containing lactic or glycolic acid residues) are also well known in the art. See, e.g., U.S. Patent Nos. 3,773,919 and 4,767,628 and PCT Publication No. WO 94/15587.

The somatostatin or somatostatin agonist may also be administered with another compound capable of lowering blood levels of triglycerides, cholesterol, or glycerol, such as fibrates (e.g., bezafibrate, gemfibrozil, and clofibrate), HMG-COA reductase inhibitors (e.g., pravastatin, simvastatin, and fluorastatin, Atorvastatin, and Lovastatin), bile cid binding resins (e.g., cholestyramine and colestipol), nicotinic acid compounds (e.g., nicotinic acid and niceritrol), and fish oils. See Workshop Treatment of Hyperlipidemia 1996-2 (Lakemedelsverket, Uppsala, Sweden, 1996).

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

It is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents, and other references mentioned herein are incorporated by reference.

Somatostatin and its Agonists

Somatostatin (somatotropin release inhibiting factor or SRIF) has both a 14 amino acid isoform (somatostatin-14) and a 28 amino acid isoform (somatostatin-28). See Wilson, J. & Foster, D., *Williams Textbook of Endocrinology*, p. 510 (7th ed., 1985). The compound is an inhibitor of secretion of the growth hormone and was originally isolated from the hypothalamus. Brazeau, et al., Science 179:77 (1973). Native somatostatin has a very short duration of effect *in vivo* since it is rapidly inactivated by endo- and exopeptidase. Many novel analogs (e.g., peptide and non-

peptide compounds) have been prepared in order to enhance the duration of effect, biological activity, and selectivity (e.g., for the particular somatostatin receptor) of this hormone. Such analogs of somatostatin will be called "somatostatin agonists" herein.

Various somatostatin receptors (SSTRs) have been isolated, e.g., SSTR-1, SSTR-2, SSTR-3, SSTR-4, and SSTR-5. Thus, the somatostatin agonist may be a SSTR-1 agonist, SSTR-2 agonist, SSTR-3 agonist, SSTR-4 agonist of a SSTR-5 agonist. What is meant by a somatostatin type-5 receptor agonist (i.e., SSTR-5 agonist) is a compound which (1) has a high binding affinity (e.g., Ki of less than 5 nM or preferably less than 2 nm or less than 1 nM) for SSTR-5 (e.g., as defined by the receptor binding assay described below) and (2) decreases lipid levels (e.g., cholesterol, glycerols, or triacylglycerols) in a patient (e.g., as shown by the biological assay described below). What is meant by a somatostatin type-5 receptor selective agonist is a somatostatin agonist which (1) has a higher binding affinity (i.e., Ki) for SSTR-5 than for either SSTR-1, SSTR-2, SSTR-3, or SSTR-4 and (2) decreases lipid levels (e.g., cholesterol, glycerols, or triacylglycerols) in a patient (e.g., as shown by the biological assay described below). In one embodiment, the SSTR-5 selective agonist has a Ki for SSTR-5 that is at least 2 times (e.g., at least 5 times or at least 10 times) less than its Ki for the SSTR-2 receptor (e.g., as defined by the receptor binding assay described below). In one embodiment, the

somatostatin type-5 receptor selective agonist is also a SSTR-5 agonist.

Examples of somatostatin agonists are those covered by formulae or those specifically recited in the publications set forth below, all of which are hereby incorporated by reference.

EP Application No. P5 164 EU (Inventor: G. Keri);

Van Binst, G. et al. Peptide Research 5:8 (1992);

Horvath, A. et al. Abstract, "Conformations of Somatostatin Analogs Having Antitumor Activity", 22nd European peptide Symposium, September 13-19, 1992, Interlaken, Switzerland;

PCT Application No. WO 91/09056 (1991);

EP Application No. 0 363 589 A2 (1990);

U.S. Patent No. 4,904,642 (1990);

U.S. Patent No. 4,871,717 (1989);

U.S. Patent No. 4,853,371 (1989);

U.S. Patent No. 4,725,577 (1988);

U.S. Patent No. 4,684,620 (1987);

U.S. Patent No. 4,650,787 (1987);

U.S. Patent No. 4,603,120 (1986);

U.S. Patent No. 4,585,755 (1986);

EP Application No. 0 203 031 A2 (1986);

U.S. Patent No. 4,522,813 (1985);

U.S. Patent No. 4,486,415 (1984);

U.S. Patent No. 4,485,101 (1984);

U.S. Patent No. 4,435,385 (1984);

U.S. Patent No. 4,395,403 (1983);

U.S. Patent No. 4,369,179 (1983);

U.S. Patent No. 4,360,516 (1982);

U.S. Patent No. 4,358,439 (1982);

U.S. Patent No. 4,328,214 (1982);

U.S. Patent No. 4,316,890 (1982);

U.S. Patent No. 4,310,518 (1982);

U.S. Patent No. 4,291,022 (1981);

U.S. Patent No. 4,238,481 (1980);

U.S. Patent No. 4,235,886 (1980);

U.S. Patent No. 4,224,199 (1980);

U.S. Patent No. 4,211,693 (1980);

U.S. Patent No. 4,190,648 (1980);

U.S. Patent No. 4,146,612 (1979);

U.S. Patent No. 4,133,782 (1979);

U.S. Patent No. 5,506,339 (1996);

U.S. Patent No. 4,261,885 (1981);

U.S. Patent No. 4,728,638 (1988);

U.S. Patent No. 4,282,143 (1981);

U.S. Patent No. 4,215,039 (1980);

U.S. Patent No. 4,209,426 (1980);

U.S. Patent No. 4,190,575 (1980);

EP Patent No. 0 389 180 (1990);

EP Application No. 0 505 680 (1982);

EP Application No. 0 083 305 (1982);

EP Application No. 0 030 920 (1980);

PCT Application No. WO 88/05052 (1988);

PCT Application No. WO 90/12811 (1990);

PCT Application No. WO 97/01579 (1997);

PCT Application No. WO 91/18016 (1991);

U.K. Application No. GB 2,095,261 (1981); and

French Application No. FR 2,522,655 (1983).

Examples of SSTR-5 selective somatostatin agonists include, but are not limited to, the following somatostatin analogs which are disclosed in the above-cited references:

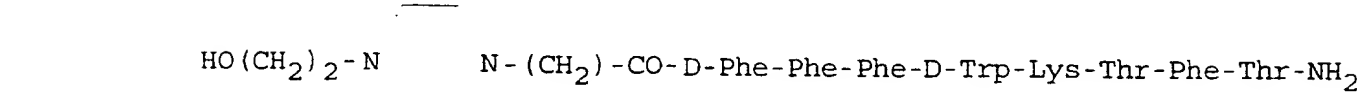
H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2 (BIM-23268);

H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2 (BIM-23052);

H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 (BIM-23284);

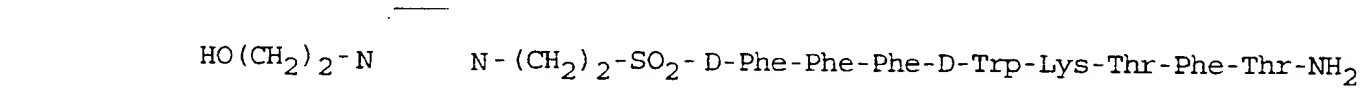
H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 (BIM-23295);

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2(BIM-23313);



$HO(CH_2)_2$-N N-(CH_2)-CO-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

(BIM-23272); and



$HO(CH_2)_2$-N N-$(CH_2)_2$-SO_2-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

Note that for all somatostatin agonists described herein, each amino acid residue represents the structure of -NH-C(R)H-CO-, in which R is the side chain (e.g., CH_3 for Ala). Lines between amino acid residues represent peptide bonds which join the amino acids. Also, where the amino acid residue is optically active, it is the L-form configuration that is intended unless D-form is expressly designated. A disulfide bond (e.g., a disulfide bridge) exists between the two free thiols of the Cys residues; however, it is not shown.

Synthesis of somatostatin agonists

The methods for synthesizing somatostatin agonists is well documented and are within the ability of a person of ordinary skill in the art.

Synthesis of short amino acid sequences is well established in the peptide art. For example, synthesis of H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2, described above, can be achieved by following the protocol set forth in Example I of European Patent Application 0 395 417 A1. The synthesis of somatostatin agonists with a substituted N-terminus can be achieved, for example, by following the protocol set forth in WO 88/02756, European Patent Application No. 0 329 295, and PCT Publication No. WO 94/04752.

Somatostatin Receptor Binding Assays

The human SSTR-1, SSTR-2, SSTR-3, SSTR-4, and SSTR-5 cDNA clones have been described (SSTR-1 and SSTR-2 in Yamada, Y., et al., Proc. Natl. Acad. Sci. USA., 89:251-255 (1992); SSTR-3 in Yamada, et al., Mol. Endocrinol. 6:2136-2142 (1993); and SSTR-4 and SSTR-5 in Yamada, et al., Biochem. Biophys. Res. Commun. 195:844-852 (1993)) and are also available from American Type Culture Collection (ATCC, Rockville, MD) (ATCC Nos. 79044 (SSTR-1), 79046 (SSTR-2), and 79048 (SSTR-3)). Based on the restriction endonuclease maps, the entire coding region of each SSTR cDNA may be excised by suitable restriction endonuclease digestion (Maniatis, T., et al., *Molecular Cloning - A Laboratory Manual,* CSHL, 1982). Restriction endonucleases are available from New England Biolabs (Beverly, MA). This cDNA fragment was inserted into the mammalian expression vector, pCMV (Russell, D., et al., J. Biol. Chem., 264:8222-8229 (1989)), using standard molecular biology techniques (see e.g., Maniatis, T., et al., Molecular Cloning,-A Laboratory

Manual, Cold Spring Harbor Laboratory, 1982) to produce the expression plasmid, pCMV-human SSTR-1 through pCMV-human SSTR-5. Other mammalian expression vectors include pcDNA1/Amp (Invitrogen, Sandlesy, CA). The expression plasmids were introduced into the suitable bacterial host, E. Coli HB101 (Stratagene, La Jolla, CA) and plasmid DNAs, for transfection, were prepared on Cesium Chloride gradients.

CHO-K1 (ovary, Chinese hamster) cells were obtained from ATCC (ATCC No. CCL 61). The cells were grown and maintained in Ham's F12 media (Gibco BRL, Grand Island, NY) supplemented with 10% fetal bovine serum under standard tissue culture conditions. For transfection, the cells were seeded at a density 1 x 10^6/60-cm plate (Baxter Scientific Products, McGraw Park, IL.). DNA mediated transfection was carried out using the calcium phosphate co-precipitation method (Ausubel, F.M., et al., Current Protocols in Molecular Biology, John Wiley & Sons, 1987). The plasmid pRSV-neo (ATCC; ATCC No. 37198) was included as a selectable marker at 1/10 the concentration of the expression plasmid. CHO-K1 clonal cell lines that have stably inherited the transfected DNA were selected for growth in Ham's F12 media containing 10% fetal bovine serum and 0.5mg/ml of G418 (Sigma). The cells were ring-cloned and expanded in the same media for analysis.

Expression of the human SSTR-1 through SSTR-5 receptors in the CHO-K1 cells were detected by Northern blot analysis of total RNA prepared from the cells (Sambrook, J.E., et al., Molecular Cloning - A Laboratory

Manual, Ed. 2., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1989) and by receptor binding using [^{125}I-Tyr^{11}]somatostatin-14 as a ligand. Transfected cell lines expressing the human SSTR receptors were clonally expanded in culture and used in the following SSTR binding protocol.

Crude membranes were prepared by homogenization of the transfected cells in 20 ml of ice-cold 50 mM Tris-HCl with a POLYTRON homogenizer (setting 6, 15 sec). Buffer was added to obtain a final volume of 40 ml, and the homogenate was centrifuged in a Sorval SS-34 rotor at 39,000 g for 10 min at 0-4°C. The resulting supernatant was decanted and discarded. The pellet was rehomogenized in ice-cold buffer, diluted, and centrifuged as before. The final pellet was resuspended in the 10 mM Tris HCl and held on ice for the receptor binding assay.

Aliquots of the membrane preparation were incubated for 30 min at 30°C with 0.05 nM [^{125}I-Tyr^{11}]somatostatin-14 (2000 Ci/mmol; Amersham Corp., Arlington Heights, IL) in 50 mM HEPES (pH 7.4) containing a test somatostatin agonist of various concentrations (e.g., 10^{-11} to 10^{-6}), 10 mg/ml bovine serum albumin (fraction V) (Sigma Chemical Co., St. Louis, MO), $MgCl_2$ (5 mM), Trasylol (200 KIU ml), bacitracin (0.02 mg/ml), and phenylmethylsulphonyl fluoride (0.02 mg/ml). The final assay volume was 0.3 ml. The incubations were terminated by rapid filtration through GF/C filters (pre-soaked in 0.3% polyethylenimine for 30 min) using a Brandel filtration manifold. Each tube and filter were then

washed three times with 5 ml aliquots of ice-cold buffer. Specific binding was defined as the total [^{125}I-Tyr^{11}]SRIF-14 bound minus that bound in the presence of 1000 nM. The Ki values for the tested somatostatin agonists were calculated by using the following formula: $Ki = IC_{50} / [1+(LC/LEC)]$ where IC_{50} is the concentration of test somatostatin agonist required to inhibit 50 percent of the specific binding of the radioligand [^{125}I-Tyr^{11}]somatostatin-14, LC is the concentration of the radioligand (0.05 nM), and LEC is the equilibrium dissociation constant of the radioligand (0.16 nM). The Ki values (nm) for the tested somatostatin agonists are shown in Table I.

TABLE I

	hSSTR-1	hSSTR-2	hSSTR-3	hSSTR-4	hSSTR-5
Somatostatin-14	2.26	0.23	1.2	1.8	1.41
Somatostatin-28	2.38	0.30	1.3	7.93	0.4
BIM-23268	1227	15.06	545	3551	0.42
BIM-23052	97.6	11.96	5.6	127	1.22
BIM-23272	47.7	3.23	10.9	753	1.01
BIM-23284	27.9	19.3	35.6	58.6	0.85
BIM-23295	86.9	6.19	9.7	3.4	0.34
BIM-23313	151	4.78	25.5	55.3	0.30

Reduction of Glycerol and Triglycerides

The obese (fa/fa) Zucker and its derivative in the Zucker diabetic fatty (ZDF/Drt-fa) are excellent models of diabetes-induced dyspilidemia (Shafrir, E., Diabetes/Metabolism Rev. 8:179-208 (1992); Peterson,

R.G., et al., ILAR News 32:16-19 (1990)). The animals develop progressive hypertriglyceridemia and hypercholesterolemia.

The effect of chronic treatment with BIM-23268 on plasma lipids was examined in an obese animal model, the fatty (fa/fa) Zucker rats (Bray, G., Federation Proceedings 36:q48-153 (1977)) (purchased from Harlan-Olac, Bicester, Oxon, U.K.). Eleven male fatty Zucker rats weighing about 450 grams were randomly divided into 2 groups and their initial body weights recorded. The animals were housed in pairs in a normal 12 hour light/dark cycle at 20 " 21C and fed a standard laboratory rat diet (Beekay rat and mouse diet, Bantin & Kingman, Hull, Humberside, U.K.) overnight *ad libitum*.

± °C

For the group assigned to receive drug treatment, the rats received BIM-23268C at 3 mg/kg, by subcutaneous injection twice a day at 10:00 a.m. and 5:00 p.m. The other group was treated with a subcutaneous injection of 0.1 ml/100 g of saline twice a day at 10:00 a.m. and 5:00 p.m. The animals were subjected to the BIM-23268 or saline treatment for a total of six days.

On the last day of treatment (day 6), food was removed at 5:00 p.m. and the rats fasted overnight. At 9:00 a.m. the next day, the animals were subjected to a glucose challenge, given as a 0.8 gram/kg of glucose orally. Periodic 400 ul of blood samples were taken from the tail vein (Peterson, R.G., ILAR News 32:16-19 (1990)) at 60 min. and 30 min. before, and at 30, 60, 90, and 120 min. after the administration of the glucose challenge (08. gram/kg orally). Aprotinin (Traysylol, Bayer UK,

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Hayward's Heath, W. Sussex, U.K.) and heparin (Sigma Chemical Co., Poole, Dorset, U.K.) were added to the blood samples to a final concentration of 400 KIU/ml and 100 units/ml, respectively. Plasma fractions were prepared from these samples by centrifugation at 400 x G in a microfuge, for the estimation of triglycerides and glycerol. Samples were then stored at -801C until assayed.

Plasma glycerol and triglycerides were determined using the Sigma Enzymatic (Tinder) calorimetric assay kit (Cat #337-B, Sigma Chemical Co., Poole, Dorset, U.K.) and measuring absorbance at 540 nm in a spectrophotometer.

After 6 days of treatment with BIM-23268C at 3 mg/kg, twice a day by subcutaneous injection, both plasma glycerol and triglycerides were significantly lowered, as exemplified by the samples taken at time 30 and 60 min. before the oral glucose challenge. See Fig. 1 and Fig. 2. The administration of an oral glucose challenge had no significant effect on plasma lipids. The BIM-23268C treated group showed significantly lower plasma glycerol and triglycerides through the 2-hour test period. The results suggested that BIM-23268C, following a 6-day treatment period at the prescribed dose was effective in reducing hypertriglyceridemia.

Measure of Efficacy in Patient

The effect of the somatostatin agonist will be assessed for a reduction in total cholesterol, total triglycerides, and total LDL cholesterol (e.g., as described in Dubrey, S.W., et al., Diabetes 43:831-835

(1994). The long term effect of the drug is examined by the change in coronary artery disease (Reviewed in Donahue, The Endocrinologist, 4:112-116 (1994).

OTHER EMBODIMENTS

The foregoing description has been limited to specific embodiments of this invention. It will be apparent, however, that variations and modifications may be made to the invention, with the attainment of some or all of the advantages of the invention. Such embodiments are also within the scope of the following claims.

CLAIMS

1. A method of treating hyperlipidemia in a patient, said method comprising administering a therapeutically effective amount of a somatostatin type-5 receptor agonist to said patient.

2. A method of claim 1, wherein said somatostatin type-5 receptor agonist has a Ki of less than 2 nM for the somatostatin type-5 receptor.

3. A method of treating hyperlipidemia in a patient, said method comprising administering a therapeutically effective amount of a somatostatin type-5 receptor selective agonist to said patient.

4. A method of claim 3, wherein said somatostatin type-5 receptor selective agonist has a Ki for the type-5 somatostatin receptor that is at least 10 times less than its Ki for the somatostatin type-2 receptor.

5. A method of claim 1, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, where a disulfide bond exists between the free thiols of the two Cys residues, or H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2.

6. A method of lowering the amount of triacylglycerols, glycerol, or cholesterol in the blood of a patient, said method comprising administering a therapeutically effective amount of a somatostatin type-5 receptor agonist to said patient.

7. A method of lowering the amount of triacylglycerols, glycerol, or cholesterol in the blood

of a patient, said method comprising administering a therapeutically effective amount of a somatostatin type-5 receptor selective agonist to said patient.

8. A method of claim 6, wherein said method comprises lowering the amount of triacylglycerols in said patient.

9. A method of claim 8, wherein said somatostatin type-5 receptor agonist has a Ki of less than 2 nM for the somatostatin type-5 receptor.

10. A method of claim 7, wherein said method comprises lowering the amount of triacylglycerols in said patient.

11. A method of claim 10, wherein said somatostatin type-5 receptor selective agonist has a Ki for the type-5 somatostatin receptor that is at least 10 times less than its Ki for the somatostatin type-2 receptor.

12. A method of claim 8, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, where a disulfide bond exists between the free thiols of the two Cys residues, or H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2.

13. A method of claim 6, wherein said method comprises lowering the amount of glycerol in said patient.

14. A method of claim 13, wherein said somatostatin type-5 receptor agonist has a Ki of less than 2 nM for the somatostatin type-5 receptor.

15. A method of claim 7, wherein said method comprises lowering the amount of glycerol in said patient.

16. A method of claim 15, wherein said somatostatin type-5 receptor selective agonist has a Ki for the type-5 somatostatin receptor that is at least 10 times less than its Ki for the somatostatin type-2 receptor.

17. A method of claim 13, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, where a disulfide bond exists between the free thiols of the two Cys residues, or H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2.

18. A method of claim 6, wherein said method comprises lowering the amount of cholesterol in said patient.

19. A method of claim 18, wherein said somatostatin type-5 receptor agonist has a Ki of less than 2 nM for the somatostatin type-5 receptor.

20. A method of claim 7, wherein said method comprises lowering the amount of total cholesterol or LDL cholesterol in said patient.

21. A method of claim 20, wherein said somatostatin type-5 receptor selective agonist has a Ki for the type-5 somatostatin receptor that is at least 10 times less than its Ki for the somatostatin type-2 receptor.

22. A method of claim 18, said method comprising administering a therapeutically effective amount of H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH_2, where a disulfide

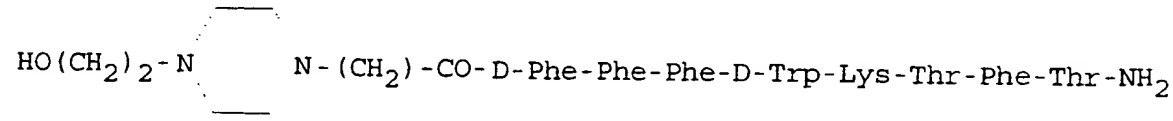
bond exists between the free thiols of the two Cys residues, or H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2.

23. A method according to claim 1 wherein the somatostatin type-5 receptor agonist is

H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,



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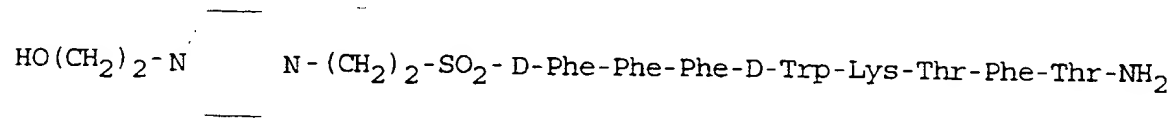
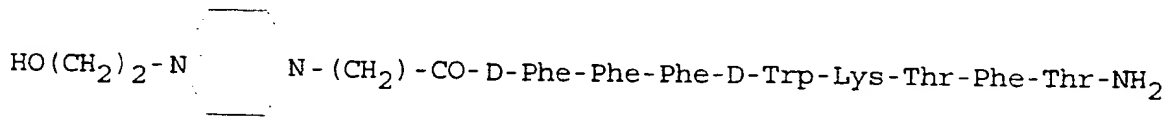


24. A method according to claim 8 wherein the somatostatin type-5 receptor agonist is

H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,



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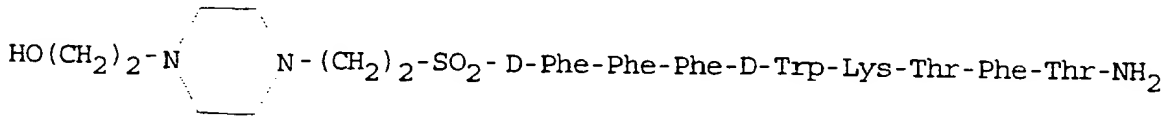
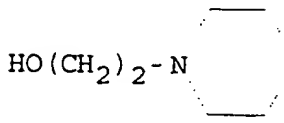


25. A method according to claim 13 wherein the somatostatin type-5 receptor agonist is

H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,

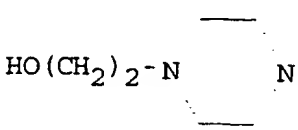
H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,



$HO(CH_2)_2$-N N-(CH_2)-CO-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

or



$HO(CH_2)_2$-N N-$(CH_2)_2$-SO_2-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

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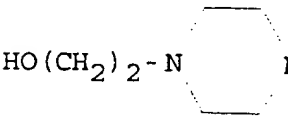
26. A method according to claim 18 wherein the somatostatin type-5 receptor agonist is

H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH_2 ,

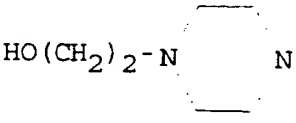
H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,

H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH_2 ,



$HO(CH_2)_2$-N N-(CH_2)-CO-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

or



$HO(CH_2)_2$-N N-$(CH_2)_2$-SO_2-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

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27. A pharmaceutical composition comprising a therapeutically effective amount of a somatostatin type-5 receptor, optionally selective, agonist.

28. A pharmaceutical composition as claimed in claim 27, said agonist having the features identified in any one of claims 2, 4, 5 and 23 to 26.

29. Use of a somatostatin type-5 receptor, optinally selective, agonist in the formulation of a pharmaceutical composition for use in treating hyperlipidemia, or reducing the amount of

tracylglycerols, glycerol, or cholesterol in a human or mammalian animal.

30. Use of a somatostatin agonist according to claim 29, wherein said somatostatin agonist has the relevant features identified in any one of claims 2, 4, 5 and 23 to 26.

31. A pharmaceutical composition substantially as hereinbefore described with reference to the Examples.